Attorney Docket No. 1909.03 PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors: Wettstein et al.	
Application No.: 10/099,924	
	Group Art Unit: 1643
Filed: March 14, 2002	
	Examiner: A. Harris, Ph.D.
For: SURVIVIN-INTERACTING PROTEINS AND USE THEREOF	

REPLY TO EXAMINER'S ANSWER (37 C.F.R. § 41.41)

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Commissioner for Patents
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Sir:

Appellants submit this Reply Brief, in accordance with 37 C.F.R. § 41.41, less than two months from the mailing of Examiner's Answer dated August 24, 2006.

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(1) STATUS OF CLAIMS

Claims 40 – 50 are currently pending in the Application. Claims 1 – 10, 18 – 19, 27 – 39 have been cancelled. Claims 11 – 17 and 20 – 26 are withdrawn from consideration. Claims 40 – 50 were finally rejected in a Final Office Action mailed on September 1, 2005, and are being appealed. Of these eleven appealed claims, only two (40 and 45) are independent claims.

(2) STATUS OF AMENDMENTS

Appellants filed an Amendment on November 1, 2005 to correct minor typographical errors, one in the Specification and one in Claim 44. The Advisory Action of January 23, 2006 stated that these Amendments were not entered because they allegedly introduced new issues and new matter. Appellants respectfully traverse this refusal to enter the Amendment and provide reasons below.

(3) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

1. Whether claims 40 – 50 are unpatentable under 35 USC § 112, first paragraph, as representing new matter not supported in the specification.
2. Whether claims 40 – 50 are unpatentable under 35 USC § 112, first paragraph, as being based on a disclosure with insufficient written description.
3. Whether claims 40 – 50 are unpatentable under 35 USC § 112, first paragraph as being based on a nonenabling disclosure.

(4) ARGUMENT

As is clear from the Grounds of Rejection section above, the pending claims stand finally rejected as being based upon a disclosure that allegedly provides insufficient written description, on the grounds of alleged indefiniteness, and on the grounds of alleged anticipation. In general, Examiner's Answer simply repeats the allegations contained in the Final Rejection. Appellants thoroughly dealt with these allegations in the Appeal Brief and so no detailed discussion will be given here. To the extent the Answer raises new arguments, allegations, or evidence, however, Appellants respond below.

A. Amendment of November 1, 2005

As an initial matter, Examiner's Advisory Action of January 23, 2006 states that Appellants' Amendment of November 1, 2005 has not been entered because it introduces new issues and new matter. As support for such an allegation, the Advisory Action responds to Appellants' substantive arguments regarding the Amendments of April 4, 2005 and May 5, 2005. No explanation is given in support of the allegation that the Amendment of November 1, 2005, substituting "screen" for "screening" in the Specification (p. 4, l. 31) and "Claim" for "claim" in Claim 44, introduces new issues or new matter. Appellants request that the Amendments of November 1, 2005 be entered as they correct obvious errors and do not introduce any new issues or new matter.

B. Rejection under 35 USC § 112, first paragraph – written description

Claims 40 – 50 are finally rejected under 35 USC § 112, first paragraph as being based upon a disclosure that allegedly lacks sufficient written description of the invention. In order to support a written description rejection, the examiner must present prima facie evidence that one skilled in the art could not reasonably conclude that the applicant was in possession of the claimed subject matter. Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563 (Fed. Cir. 1991).

Examiner's Answer repeats the allegations in the Final Rejection, which have been treated at length in the Appeal Brief. Specifically, the Answer alleges: (1) Claims 40 – 50, added by amendment, are not supported by the Specification or the original claims and thus represent new matter, Examiner's Answer, pp. 10 – 12; (2) the USPTO's Written Description Guidelines are not binding law and, in essence, Federal Circuit case law is not binding either, id. at p. 13, first paragraph, p. 14, second paragraph; and (3) "Appellant has not exemplified support or contemplation for all the possible peptide combinations comprised within the claimed isolated protein complex or fusion proteins that are encompassed by the claims," id. at p. 13, second paragraph (emphasis added). These allegations will be dealt with in turn.

1. New Matter Rejection

Examiner's Answer alleges that the following claim limitations lack support in the as-filed Specification: a "polypeptide having an amino acid sequence at least 80% identical" to either survivin or HDLC1 fragments (Claim 40); "fragment of survivin compris[ing] amino acid residues ... 47 to 99 of survivin" (Claim 43); survivin or HDLC "fragment[s] comprising a contiguous span of 10 amino acid residues" of native survivin or HDLC1 (Claim 45); a "polypeptide having an amino acid sequence at least 90% identical" to either native survivin or native HDLC1 (Claim 45); a polypeptide that has an amino acid sequence at least 80% or 90% identical to specific regions of survivin (Claims 49 and 50). Examiner further alleges that Appellants did not point to support for these elements in the Remarks submitted April 4, 2005 and May 5, 2005. While no element-by-element analysis was submitted in the April 4, 2005 and May 5, 2005 Amendments that added Claims 49 – 49, Appellants supplied just such an analysis in their response of November 1, 2005. In fact, this element-by-element accounting was reproduced in the Appeal Brief on p. 6.

The Advisory Action of January 23, 2006 makes only conclusory allegations regarding support for the above language without any explanation as to why the remarks of the November 1, 2005 Amendment are allegedly insufficient. For example, the Advisory Action alleges that the Specification does not have support for polypeptides that are 80% identical to fragments of survivin (as opposed to native or full-length survivin). The Advisory Action posits that such fragments could be "as little as 2 or 3 amino acid residues."

Such a reading of the claim ignores the claim language as well as the crux of Appellants' discovery: the interaction between survivin and HDLC1. Claim 40 indeed recites a polypeptide at least 80% identical to "survivin or fragments thereof." "Fragments thereof," however, are limited in Claim 40 to those fragments that "**interact with HDLC1**." Thus Examiner's hypothetical 3 amino acid fragment would only fall within Claim 40 if it **interacted with HDLC1**, which is most unlikely.

Homologues of fragments are contemplated in the as-filed Specification. A "protein fragment" is defined to include a "portion of a protein" which may interact with another protein or protein fragment "through interaction domains that are contained

within the [proteins or fragments]." Specification, p. 15, ll. 1 – 4. "'Interaction domain' refers specifically to a portion, segment or region of a protein, polypeptide or protein fragment that is responsible for the physical affinity of that protein, protein fragment or isolated domain for another protein, protein fragment or isolated domain." Id. at p. 15, ll. 6 – 9. Thus "interaction domains" may include **segments** of a full-length protein, which could include protein **fragments**. And finally "homologue" "means a polypeptide that exhibits an amino acid sequence homology and/or structural resemblance to the first native interacting protein, **or to one of the interacting domains of the first native protein** such that it is capable of interacting with the second native protein." Id. at p. 17, ll. 8 – 11. "Homologue" is thus defined broadly to include any polypeptide that shares sequence identity with **either** the full-length, native protein **or** an interacting domain of that native protein. Protein fragments may fall within this definition because they are polypeptides that may contain interaction domains that share sequence identity or structural similarity with interaction domains of native survivin (i.e. they fulfill the minimal requirements of the definition of "homologue"). Thus fragment homologues are fully contemplated, hence supported, in the as-filed Specification.

Appellants yet again point out specific portions of the as-filed Specification that support each of the other elements objected to in Examiner's Answer:

(1) "fragment of survivin compris[ing] amino acid residues ... 47 to 99 of survivin" (Claim 43): Table 1 of the Specification lists three different survivin fragments that interact with HDLC1. Specification, p. 21, Table 1. These include residues 89 –143, 3 – 99, and 47 – 143. Anyone skilled in the art would immediately recognize from this that the interaction domain of survivin (responsible for the interaction with HDLC1) is probably within amino acid residues 47 – 99. Thus, by showing the overlap between these fragments and claiming fragments comprising this overlapping region, Appellants have fully described and supported this limitation.

(2) survivin or HDLC "fragment[s] comprising a contiguous span of 10 amino acid residues" of native survivin or HDLC1 (Claim 45): Specification explicitly contemplates such fragments. Id. at p. 96, l. 28 – p. 97, l. 2; p. 97,

ll. 7 – 16; p. 27, l. 30 – p. 28, l. 12. Examiner has not explained why these portions of the Specification are insufficient to support the above claim limitation.

(3) "polypeptide having an amino acid sequence at least 90% identical" to either native survivin or native HDLC1 (Claim 45): unlike the first limitation discussed above, this claim is directed specifically to fragments of native survivin or native HDLC1. See Specification, Claim 45, limitations (a) and (i). Regardless, homologues of fragments are contemplated in the Specification as shown above.

(4) polypeptide that has an amino acid sequence at least 80% or 90% identical to specific regions (residues 89-142, 3-99, 47-142 or 47-99) of survivin (Claims 49 and 50): as discussed above, "homologue" is defined in the Specification to include a polypeptide that exhibits an amino acid sequence homology and/or structural resemblance to the first native interacting protein, **or to one of the interacting domains of the first native protein**." Specification, p. 17, ll. 8 – 11. The recited residues represent probable interacting domains of survivin. Thus the explicit definition of "homologue" in the Specification contemplates polypeptides that show sequence or structural homology to these specific regions of survivin.

Appellants respectfully request that the new matter rejection be reversed.

2. Written Description Guidelines and Federal Circuit Case Law

Examiner's Answer reminds Appellants that the USPTO's Written Description Guidelines ("Guidelines") are not binding law and alleges that these "should not be considered as information to support an argument." Examiner's Answer, p. 13, first paragraph.

Appellants acknowledged in the Appeal Brief that the Guidelines are not binding law, as this is clearly stated in the Manual of Patent Examination Procedure. MPEP § 2163, pp. 2100-171 – 2100-172 (Rev. 3 August 2005). Appellants' discussion of the Guidelines in the Appeal Brief was intended, as the MPEP indicates, "to assist [the

Examiner] in analyzing claimed subject matter for compliance with substantive law." Id. Appellants hereby clarify that Examiner's failure to follow the Guidelines, while unfortunate, is not what is being appealed. Examiner's failure to correctly apply substantive patent law in examining the instant application is being appealed. As noted in the Appeal Brief, discussion of the Guidelines is warranted because the Federal Circuit has explicitly incorporated the Guidelines into its substantive jurisprudence. See Enzo Biochem Inc. v. Gen-Probe, Inc. 323 F.3d 956, 964 (Fed. Cir. 2005.

Examiner's Answer further dismisses the Appeal Brief's discussion of Federal Circuit case law such as Invitrogen. Examiner's Answer, p. 12, last paragraph, p. 14, second paragraph. Examiner vaguely alleges that the present case is distinguishable from Invitrogen, but gives no specific reasons supporting this allegation other than the general statement "each case or application has its own individuality and judgments and rejections are based on the particulars of each case." Id. at p. 14, second paragraph.

By disregarding binding Federal Circuit case law and failing to address Appellants' arguments demonstrating its applicability to the present application, Examiner has in essence denied its binding effect on the examination process. The Court of Appeals for the Federal Circuit interprets statutory law in the field of patents and its decisions become, as noted by the MPEP, "binding precedent" on Office personnel examining patents. MPEP § 2163, pp. 2100-171 (Rev. 3 August 2005). It is true that no valid case, either in a court or before an administrative agency, presents facts that are absolutely identical to any other. Stare decisis and legal reasoning are, at their core, the process of analogizing a past decision based on an earlier set of facts to the present set of similar facts. Invitrogen represents a Federal Circuit decision in which a claim to a genus at least as broad as Appellants' and similarly defined – by structural and functional limitations – was held sufficiently described. The striking similarity in the facts of these two cases cries out for allowance of the present claims and Appellants respectfully submit that Examiner's refusal to follow binding precedent is improper.

3. Appellants Have Disclosed Sufficient Structural and Functional Limitations to Describe the Entire Claimed Genus

The heart of the written description issue in this case is whether one skilled in the art could reasonably conclude that Appellants were in possession of the genus of protein complexes encompassed by Claims 40 and 45. Examiner has confused this issue by contending that Appellants must enumerate in the Specification every possible modification of survivin and HDLC1 that retain the ability to interact. See Examiner's Answer, p. 13, second paragraph. In reality, Appellants have complied with § 112, first paragraph by giving structural and functional limitations that serve to differentiate members of the claimed genus from those of other genera.

The impropriety of Examiner's rejection can be most easily seen when its reasoning is applied to the claim at issue in Invitrogen. Under Examiner's proposed test, the patentee in Invitrogen would have needed to disclose every possible modification to the naturally occurring reverse transcriptase gene in order to claim a polypeptide encoded by "a modified reverse transcriptase nucleotide sequence." See Invitrogen, 429 F.3d at 1072. Such a result, however, would be entirely at odds with the court's actually holding in Invitrogen. The court held that disclosure of the structural (nucleotide and amino acid sequences) and functional (test data showing that one modified reverse transcriptase actually had catalytic activity) characteristics of one representative embodiment was sufficient to describe the full scope of the genus.

Examiner has given no basis for distinguishing the present case from Invitrogen because none exists. The claim at issue in Invitrogen defined a broad genus of modified reverse transcriptases in terms of **structure** (art-known proteins with only one working example disclosed in the specification) and **function** (catalyzing the reverse transcription reaction while having reduced RNaseH catalytic activity). Claim 40, for example, also defines the claimed genus in terms of **structure** (identity to survivin or HDLC1, both well known proteins in the art, and at least three working examples disclosed in the Specification) and **function** (ability of native proteins, homologues, fragments, homologues of fragments, and fusions to interact with survivin or HDLC1). The similarities are glaring, whereas any supposed distinction is artificial at best.

Because Appellants' Specification more than complies with the requirements of § 112, first paragraph as mandated by Invitrogen, Appellants request that Examiner's rejection be reversed.

C. Rejection under 35 USC § 112 – enablement

Examiner's Answer continues to allege that Claims 40 – 50 lack enablement. Examiner's Answer, pp. 14 – 16. Examiner's primary allegation in this regard is that the Specification lacks guidance sufficient to allow one skilled in the art to make homologues, fragments, and homologues of fragments of survivin and HDLC1 that retain the ability to interact. Id. at p. 15, first paragraph. Appellants respectfully disagree.

Enablement is lacking only if one skilled in the art would be unable to practice the invention without engaging in undue experimentation. In re Wands, 858 F.2d 731, 736-737 (Fed. Cir. 1988). "A considerable amount of experimentation is permissible, if it is merely routine, **or** if the specification [gives] a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." Id. at 737 (emphasis added). Thus an applicant need only show either that the experimentation required is routine or that the specification gives reasonable guidance, but not both. As will be shown, Appellants have amply proved that both of the above alternative requirements are met in the present case, thus going beyond that which is required under In re Wands.

In re Wands is the benchmark in biotech enablement analysis. At issue was monoclonal antibody technology, specifically assays using high-affinity monoclonal antibodies to hepatitis B-surface antigen (HBsAg). Id. at 734. The Board contended claims to such assays were not enabled because screening for the high-affinity antibodies required undue experimentation. Id. at 739. More specifically, the Board pointed to what it deemed a very low success rate, which in turn meant artisans would need to undertake undue experimentation to find antibodies with the desired binding affinity. Id.

The Federal Circuit reversed the Board, however, holding that the invention could be practiced without undue experimentation. Id. at 740. The court noted that the applicant's success rate was higher than the Board contended, but more importantly the court emphasized the routine nature of the experimentation needed to obtain antibodies within the scope of the claim. Id. Even a laborious process comprising "immunizing

animals, fusing lymphocytes from the immunized animals with myeloma cells to make hybridomas, cloning the hybridomas, and screening the antibodies produced by the hybridomas for the desired characteristics" did not, in the court's estimation, represent an "excessive" amount of effort. Id. The court also found helpful the "considerable guidance" in the specification, guidance that consisted solely of instructions on how to carry out the above experiment steps. See generally, U.S. Patent No. 4,879,219 ('219 patent), which derives from the application at issue in In re Wands.

The present case is analogous to Wands in that no undue experimentation is needed because the experimentation called for is purely routine. Much like in Wands, several experimental steps must be carried out in order to find protein complexes in addition to those actual examples disclosed in the Specification that fall within Appellants' claims. See Specification, p. 30, l. 5 – p. 35, l. 15 (describing production of protein complexes); p. 34, ll. 5-27 (specifically discussing production of protein fragments and homologues); p. 118, l. 15 – p. 119, l. 24, p. 57, l. 22 – p. 58, l. 10 (discussing yeast-two hybrid system and its use in screening for interaction or disruption of interaction between protein fragments). All of these steps, however, are routine within the art. At the time of filing, for example, it was a routine task for a skilled artisan to identify proteins homologous or orthologous to survivin, and to align such proteins and identify regions of conservation. Amino acid changes outside the regions of conservation would less likely result in loss of capability of interacting. Examiner has not met the burden of showing, and indeed has only made conclusory allegations, that these steps are anything other than routine. The enablement inquiry could end here.

Just as in Wands, however, Appellants have given ample guidance on how to carry out these routine experiments. See Specification, p. 30, l. 5 – p. 35, l. 15 (describing production of protein complexes); p. 34, ll. 5-27 (specifically discussing production of protein fragments and homologues); p. 118, l. 15 – p. 119, l. 24, p. 57, l. 22 – p. 58, l. 10 (discussing yeast-two hybrid system and its use in screening for interaction or disruption of interaction between protein fragments).

In fact, Appellants have exceeded that required by Wands by describing the screening process in detail **and** providing specific guidance regarding which protein homologues and fragment homologues might form complexes. The Wands application

gives no guidance on which of the thousands of cells extracted from the immunized mouse will ultimately yield anti-HBsAg antibodies with sufficient affinity to satisfy the elements of the claim. See generally, '219 patent. Instead the application simply offers instructions and examples on how to carry out the arduous screening process needed to find high-affinity IgMs. Id. Appellants, in contrast, have gone further, giving artisans a starting point for finding interacting homologues and fragments by indicating probable binding regions of both survivin and HDLC1. Specification, p. 21 (Table 1: Binding Regions of Survivin and Its Interacting Partners); p. 27, ll. 20-25; p. 29, ll. 6-14. Examiner has given no reasoned basis for doubting that this guidance represents a "reasonable amount of guidance with respect to the direction in which the experimentation should proceed." Wands, 858 F.2d at 737.

Thus, given the Specification's description of art-routine experiments and its directions regarding which amino acid positions might be tolerant of substitution, one of ordinary skill in the art would know how to (1) perform alignments of amino acid sequences of homologous proteins, (2) identify conserved amino acid residues, (3) introduce conservative changes to specific residues in regions of proteins not exhibiting significant conservation, and (4) test whether the engineered variant proteins are still capable of interacting.

In sum, while it is true that an extended time and effort might be required to identify all possible survivin and HDLC1 fragments and homologues within the scope of the claims, "the mere fact that the experimentation may have been difficult and time consuming does not mandate a conclusion that such experimentation would have been considered to be 'undue' in the art." Falkner v. Inglis, 448 F.3d 1357, 1365 (Fed. Cir. 2006) (quoting Board Op.). Appellants therefore ask that Examiner's rejection on this point be reversed.

(5) CONCLUSION

All claims are in condition for allowance. The Board is requested to reverse all rejections by the Examiner.

Therefore, it is believed that no other extension of time, nor any additional fees, are due with this brief. If this is incorrect, an extension of time as deemed necessary is hereby requested, and the Commissioner is hereby authorized to charge any appropriate fees or deficiency, or credit any overpayment, to Deposit Account no. **50-1627**.

Respectfully submitted,

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